

# Deep dive into diabetes and infection

People with diabetes have a 1.5- to 4-fold increased risk of infections compared to those without diabetes, and have poorer outcomes including increased mortality, according to this review by Richard Holt and colleagues published in *Diabetologia*. Kidney infections, osteomyelitis, foot infections, pneumonia, influenza, tuberculosis, skin infections and general sepsis are common and of concern. In addition, some infections and their treatments may increase the risk of diabetes and hyperglycaemia. Hyperglycaemia affects both the innate and adaptive parts of the immune system, and people with diabetes often have altered skin and mucosal flora, and altered microbiome, which can contribute to increased infection risk and poorer outcomes. The pandemic brought this association between diabetes and infection clearly into focus, reminding us of the importance of COVID-19, influenza and pneumococcal vaccines for people with diabetes. A high index of suspicion, early diagnosis and prompt treatment, using the same drugs as in people without diabetes, are important if we are to reduce risks from infections in people with diabetes.

Although it has long been recognised that infection is more common and may be more severe in people with diabetes, this remained a relatively understudied complication of diabetes until the COVID-19 pandemic, according to this review by Richard Holt and colleagues, published in *Diabetologia* (Holt et al. 2024).

Infections can also impact glycaemia through effects on insulin secretion and insulin resistance, resulting in increased risk of diabetes, and can trigger diabetic ketoacidosis and hyperosmolar hyperglycaemic state in those with diabetes. Infection causes a stress reaction, which triggers increases in counter-regulatory hormones (glucagon, growth hormone, catecholamines and glucocorticoids) and inflammatory cytokines, all of which antagonise insulin and impair glucose uptake to skeletal muscle. For example, gingivitis and periodontitis bacterial infections trigger inflammation and can increase risk of diabetes and of hyperglycaemia, and effective treatment can improve HbA<sub>1c</sub> by 3–6 mmol/mol after 3 months.

People with diabetes have a 2–4-fold increased risk of hospitalisation for infection and a 1.5-fold increased risk of outpatient infections compared to those without diabetes. Risks are greatest for kidney infection (up to almost five times higher in those with diabetes) osteomyelitis (4–15 times higher) and foot infection (6–15 times higher). Risks of pneumonia, flu, tuberculosis, skin

infections, surgical infections and general sepsis are also higher. Infection outcomes are also worse, including a doubling of the death rates from COVID-19 in those with diabetes.

The risk differences are greatest in younger versus older people, but are not significantly associated with ethnicity. Where risks are separated for those with type 1 versus type 2 diabetes, they are higher in people with type 1; however, most data reports both types combined. Hyperglycaemia and obesity may both increase risk of infection, but the association with HbA<sub>1c</sub> is strongest for tuberculosis and kidney infections.

## Mechanisms

Many mechanisms are implicated in the increased risk of, and impaired response to, infections in people with diabetes versus those without. Host factors which increase risk include altered skin flora and gut microbiota dysbiosis, which affect colonisation of mucosa and skin; peripheral and autonomic neuropathy; and increased intestinal permeability impacting the integrity of the mucosa. Peripheral vascular disease and neuropathy increase the risk and severity of foot ulceration and infection.

Hyperglycaemia impacts both the innate and adaptive immune responses. Diabetes is an inflammatory state associated with activation of the innate immune system; however, impaired function of the complement pathway, reduced



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### Box. Infections strongly associated with diabetes.

#### Severe rare infections mainly in people with diabetes

- Malignant otitis externa – (*Pseudomonas aeruginosa*, occasionally *Aspergillus*)
- Fournier’s gangrene
- Panophthalmitis (usually post-cataract surgery) (*E. coli*, *Klebsiella*)
- Rhinocerebral mucormycosis (especially with diabetic ketoacidosis)

#### Severe forms of common infections

- Emphysematous forms of cystitis, pyelonephritis, cholecystitis

#### Infections in which diabetes is particularly significant

- Pneumonia and empyema caused by *Klebsiella*
- Liver, perinephric and psoas abscesses caused by *Klebsiella*
- Melioidosis (*Burkholderia pseudomallei*)

neutrophil migration, apoptosis and bacterial killing, and impaired killer cell function contribute to less effective response. The adaptive immune system also works less well due to impaired recruitment of antigen-presenting cells, diminished T-helper cells and reduced cytokine release. Many of these alterations in immune function also occur in prediabetes.

### Specific infections associated with diabetes

People with diabetes have a 1.3- to 2.6-fold higher risk of **community-acquired pneumonia**, with higher mortality rates compared to those without diabetes, and with risks increasing with higher HbA<sub>1c</sub> levels. *Streptococcus pneumoniae* is the commonest organism, but *Staphylococcus aureus* nasal carriage occurs in up to 30% of people with diabetes versus only 11% of those without. Both *S. aureus* and *Klebsiella pneumoniae* commonly cause pneumonia in people with diabetes.

Diabetes increases the risk of **severe influenza** leading to intensive care admission, ventilation and in-hospital death in those aged 15–50 years. Mortality can be four times greater than in those without diabetes. Influenza and bacterial pneumonia increase the risk of acute coronary events for weeks to months after the initial illness. RAAS blocker use appears to be associated with decreased hospitalisation and mortality after pneumonia or influenza in those with and without diabetes (Christiansen et al, 2020).

People with diabetes are two to three times more likely to develop **active tuberculosis** than the general population, and having diabetes worsens outcomes, with increased risk of treatment failure, relapse and death during treatment. Thus, treatment with 9 months rather than 6 months of therapy is usually recommended.

Diabetes is an important predictor of more severe **SARS-CoV 2 infection**, with higher mortality rates. Some studies have demonstrated a correlation of poor outcome with pre-admission HbA<sub>1c</sub>, although the strongest correlation was with high glucose on admission.

All types and severities of **urinary tract infection** are increased in those with diabetes, with fungal causes and organisms other than *E. coli* more common than in the general population. People with autonomic neuropathy have decreased reflex detrusor activity and may have impaired bladder sensation, resulting in bladder distension, increased residual urine volume and vesicoureteric reflux. SGLT2 inhibitor use is associated with increased risk of genital infections but not urinary tract infections (Palmer et al, 2021).

**Skin and soft tissue infections** are more common in people with diabetes. Necrotising fasciitis occurs mainly in those with diabetes, and more than half of cases of **Fournier’s gangrene** (fasciitis affecting the perineum) occur in people with diabetes, so education, a high index of suspicion and prompt diagnosis are important.

Fifty percent of **foot ulcers** are complicated by infection, with increased risk in those with recurrent or chronic ulcers. Signs of inflammation may be less obvious in those with peripheral sensory neuropathy and vascular disease. Some groups continue to have high foot ulcer and amputation rates, including younger people, those from minority ethnic backgrounds, and those with social deprivation and/or mental health problems.

### Prevention and treatment

Although hyperglycaemia can worsen infection severity and prognosis, there is no evidence that intensive blood glucose management or weight reduction decreases infection rates in people with diabetes (Critchley et al, 2018).

Treatment for infections is generally the same as in people without diabetes. Foot disease should be managed by a multidisciplinary team with expertise in newer wound management techniques, including hyperbaric oxygen, topical oxygen therapy and negative-pressure wound therapies.

### Implications for practice

- Be aware of the increased risk of infections, the common types and the potential for poorer prognosis in people with diabetes. Prompt diagnosis and management are important.
- As well as influenza vaccine, NICE recommends pneumococcal vaccination for everyone over the age of 65 years and for those with diabetes on glucose-lowering medication, and for people with cardiovascular disease or stage 4–5 chronic kidney disease at any age. We can easily audit, add alerts and optimise vaccination rates.
- Infections should be managed the same way in those with diabetes as in those without. We should be particularly careful to only use antibiotics when clinically indicated, especially in foot ulceration. Since polypharmacy is common, we should be aware of drug interactions, and remember to consider renal function when prescribing.

- Prompt diagnosis and management of foot ulceration guided by the multidisciplinary team improves outcomes, so we need to know referral pathways and how to access urgent care.
- People with diabetes are two to three times more likely to have active tuberculosis than those without. The World Health Organization recommends people newly diagnosed with tuberculosis should be screened for type 2 diabetes, since glycaemic management can improve outcomes for tuberculosis treatment.
- Ensure that those who have had bacterial pneumonia or influenza continue on optimised primary and secondary cardiovascular disease preventative treatment, including RAAS inhibitors if appropriate, due to the increased risk of acute events following these infections. ■

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**Diabetes and infection: review of the epidemiology, mechanisms and principles of treatment**

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